

# The impact of chemotherapy on cognitive outcomes in adults with primary brain tumors

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**Abstract** There is growing recognition that chemotherapy may have short and long term impact on cognitive function of cancer patients. However, the impact of chemotherapy on the cognition of adult patients with primary brain tumor has not been extensively studied. This article will review the evidence for both positive and negative impact of chemotherapy on cognitive function of adult brain tumor patients as well as potential confounding factors.

**Keywords** Cognition · Chemo-brain · Chemotherapy · Primary brain tumor · Glioblastoma · Primary CNS lymphoma · Oligodendroglioma

## Introduction

The impact of chemotherapy on cognitive outcomes of cancer survivors is increasingly recognized and frequently referred to as “chemo brain” [1]. While this concept has gained popularity it is still being defined and verified. First described in the 1980s most early reports were attributed to patients surviving aggressive therapy for breast cancer and lymphoma. Initial descriptions were largely based on self-reporting by patients who described difficulties with memory and concentration. Increasingly studies and reports have become more rigorous with prospective neuro-cognitive assessments that document pre and post treatment deficits across multiple domains [2]. Although attention, concentration and memory remain primary areas of impairment other cognitive dimensions are also recognized as having

been affected by chemotherapy such as visuo-spatial and primary visual pathways [3].

The mechanism of injury by which chemotherapy results in cognitive loss is not known and is likely to vary according to the specific agent used. In animal models increased cell death or decreased cell division in the sub-ventricular zone and dentate gyrus have been described following exposure to carmustine, cisplatin, cytarabine and methotrexate [4, 5]. These models suggest vulnerability of neural stem cell populations with resultant cognitive impact. Primary pathologic lesions including demyelination, inflammation and microvascular injury have all been postulated as mechanisms underlying neurotoxicity of therapy [6]. Synergistic injury may occur with concomitant or sequential administration of brain radiotherapy and chemotherapy because of alterations in blood brain barrier permeability and drug distributions. Finally a recent report suggests that brain volume may decrease following myeloablative chemotherapy prior to stem cell transplant in leukemia and multiple sclerosis patients [7].

While “chemo brain” is increasingly recognized in patients with cancer other than breast cancer and lymphoma the question for this manuscript is whether or not adult brain tumor patients are at risk for significant cognitive sequelae of chemotherapeutic treatment. This topic has not been extensively explored in the past in large part due to the poor prognosis of brain tumor patients and the relative lack of effective chemotherapeutic agents.

## Confounding factors

Before considering whether or not brain tumor patients suffer adverse consequences of chemotherapy administration it is important to consider the other factors that impact cognitive

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function in this patient population. Tumor location is perhaps the most obvious consideration. The majority of primary brain tumors are located in the cerebral hemispheres and have an impact on some aspect of intellectual function. Although this may be subtle or unrecognized by the patient, family and treating physician, particularly during the acute phase of diagnosis and early treatment, it may be increasingly apparent in the long-term survivor who attempts to return to work or full level of activity following successful treatment [8].

Age is a critical consideration in assessment of cognition. The average age of diagnosis for glioblastoma, the most common primary brain tumor of adults, is 60 years. Normal persons in this age range may experience some normal slowing of information processing and retrieval as well as complaints of short-term memory loss. Furthermore in older patients, co-morbidities and associated medications may have a direct or indirect impact on cognition that must be considered. Finally as MR imaging is often used as a surrogate measure of neurotoxicity it must be recognized that nonspecific white matter changes are seen with increasing frequency according to patient age. In fact, age was one of the strongest determinants of cognitive outcome in a series of 79 primary brain tumor patients assessed at UCLA [9].

The presence or absence of both seizures and anti-epileptics medications is another important consideration in the assessment of cognitive outcome. Approximately one in three brain tumor patients will have a seizure during the course of their illness and it is known that seizure activity has a direct impact on cognitive function. Furthermore the use of anti-epileptic drugs is known to cause psychomotor slowing, decreased working memory and general cognitive decline in patients with a primary brain tumor [10].

Other considerations include the presence of co-morbidities with a direct impact on the CNS such as depression and dementia. Supportive medications may also have a significant impact on cognition. Corticosteroids are likely the biggest culprit as they are the most frequently used and have a wide range of CNS impacts from mood changes (mania and depression), insomnia, psychosis and impaired memory [11, 12].

Finally the other definitive therapies used for management of the brain tumor may result in long-term cognitive sequelae. Surgical resection can alleviate acute neurologic symptoms but may also result in permanent deficit from local injury. Radiotherapy often has a delayed impact on white matter and neurons that may result in acute or delayed leukoencephalopathy with or without associated cognitive dysfunction [10, 13].

### Specific impact of chemotherapy

A number of different scenarios may be considered to assess the impact of chemotherapy on cognitive outcome of

primary brain tumor patients. Although the use of chemotherapy alone is an uncommon strategy for primary brain tumors some patients with chemosensitive PCNSL or oligodendroglioma have been successfully managed in this fashion and provide some useful observations. Combinations of chemotherapy and radiotherapy allow for insights about sequence, specific agents and high-risk populations. Finally the increasing use of neuro-cognitive testing as a prospective endpoint in some clinical trials will allow more confident analysis of the data and development of better treatment strategies in the future.

### Chemotherapy alone

#### Primary CNS lymphoma (PCNSL)

Altered mentation is one of the most frequent ways for a patient with PCNSL to present. Indeed detailed neuro-cognitive testing at baseline and prior to specific anti-tumor treatment in PCNSL demonstrates that most patients have impairment in one or more of the following domains: attention, executive function, memory, psychomotor speed or language (specifically naming or fluency) [14]. A number of small studies have now been done that specifically incorporate prospective neuro-cognitive testing as part of PCNSL clinical trials [15–21]. These studies have consistently shown that patients either remain stable or have clear cognitive improvement during the course of initial chemotherapy provided that their tumor is responding to treatment. This includes trials with alternate and intensive delivery strategies for chemotherapy such as blood brain barrier disruption and dose intensive chemotherapy used for myeloablation [16, 22]. In long term follow up of cognitive function it has been shown that PCNSL patients treated with chemotherapy alone most often remain cognitively stable although some studies have reported minor or occasional declines in attention, memory and verbal fluency [14].

One retrospective study compared cognitive outcome in PCNSL patients treated at the same institution with either chemotherapy alone or in combination with RT [23]. Twenty-four patients were treated with a combination of chemotherapy and RT while 26 patients received chemotherapy alone. When controlling for age and time from initial diagnosis the authors concluded that patients treated with chemotherapy alone had substantially less impairment than those treated with both chemotherapy and radiotherapy. Furthermore the degree of impairment in those patients treated with chemotherapy alone was more likely to be within one standard deviation of the norm suggesting a less significant impact on day-to-day functioning.

## Anaplastic oligodendroglioma

There is growing evidence to suggest that patients with anaplastic oligodendroglioma with deletion of 1p and/or 19q may be successfully treated with chemotherapy alone as initial therapy [24, 25]. One motivation for this treatment strategy comes from the fact that these tend to be young patients often with large tumors and a relatively long life expectancy. Therefore, the concept is that delaying or deferring radiotherapy might minimize cognitive impact of therapy. Despite this trend there has been little in the way of prospective cognitive assessment in this patient population.

One study that treated such patients with chemotherapy alone using a myeloablative chemotherapy regimen in place of usual consolidation radiotherapy described that 21 long-term survivors had largely returned to their pre-morbid career or level of function [26]. Two patients were noted to have impairments ascribed to tumor but possibly treatment related. A large ongoing intergroup trial in this patient population will test chemotherapy alone as an initial treatment strategy and prospective cognitive testing is incorporated as a composite primary endpoint [27].

## Low grade glioma

A recent recommendation from the EFNS–EANO task force suggests that chemotherapy alone may be used as initial therapy for patients with large residual or unresectable tumor to delay the risk of late neurotoxicity associated with large field radiotherapy, particularly when 1p and 19q loss is present, based on level B evidence [28]. Similar to patients with anaplastic oligodendroglioma, patients with low grade glioma are often in the prime of their life and may live for many years with their tumor; hence preservation of cognitive function is a critical goal of therapy. Several studies have suggested that chemotherapy may result in various clinical improvements including improved seizure control, neurologic function and quality of life [29–31]; however, detailed neurocognitive evaluation of low grade glioma patients treated with chemotherapy alone is sparse. Correa et al. included three patients treated with chemotherapy alone in a longitudinal analysis of cognitive function in low grade glioma but this subset was too small to be critically compared [32]. Increasingly there is a mandate for clinical trials in this patient population to assess cognitive function as a prospective endpoint [28, 33]. The ongoing EORTC–NCIC study for low grade glioma includes a chemotherapy alone arm and incorporates MMSE and QOL testing with one objective to assess the delayed toxicity of temozolomide alone [34]. Another ongoing cooperative group study sponsored by ECOG will assess the addition of temozolomide to radiotherapy for newly diagnosed low grade glioma; a detailed neurocognitive substudy is planned [35].

## Chemotherapy and radiotherapy

Most often patients with primary brain tumors are treated with some combination of chemotherapy and radiotherapy. These treatments may be given in sequence or concomitantly. Depending on the underlying pathology, radiotherapy dose and field, and particular chemotherapeutic agent used, a variety of different outcomes may be anticipated.

### Primary CNS lymphoma

PCNSL was one of the first primary brain tumors to herald the risk of cognitive impact of therapy. Recognition of the detrimental impact of combined chemoradiotherapy following the sequential administration of high dose MTX and whole brain radiotherapy was first described in the early 1990s. Although this combination was clearly superior to the use of radiotherapy alone in terms of disease control and potential to extend survival, with prolonged survival it became clear that survivors, particularly those over the age of 60, were at high risk of treatment related dementia [10, 14].

A detailed review of multiple studies in the literature shows diffuse impairments in cognition following standard combined therapy with high dose methotrexate and radiotherapy [14]. The pattern of cognitive deficits spans multiple domains including attention and executive functions, psychomotor speed, learning and retrieval of new information. While the direct attribution of cognitive toxicity to the individual components of therapy is not possible from this data it seems likely that the particular sequence and combination of methotrexate followed by whole brain radiotherapy is largely responsible as opposed to either component alone.

### Anaplastic oligodendroglioma

Similar to PCNSL, patients with anaplastic oligodendroglioma have the potential for prolonged survival with excellent disease control and this tumor particularly in the setting of 1p and 19q deletion is known to be sensitive to chemotherapy. Further, patients with oligodendroglioma are often younger with a median age of 30–40 and therefore are in the prime of their working and productive life making cognitive function of critical importance.

Several studies have looked at combinations of chemotherapy and radiation to optimize disease control and survival. In particular two recently published studies compared radiation alone to radiation in combination with PCV chemotherapy [36, 37]. Both studies found similar survival for each treatment arm and confirmed the prognostic impact of 1p and 19q deletion on overall survival. While neither study included cognitive function as a

prospective endpoint for patient outcomes each study examined potential surrogate endpoints, such as mini mental status examination, performance status and quality of life. The RTOG study found that MMSE and brain related quality of life were similar between the two treatment arms [38]. However in both groups these scores tended to decline overtime suggesting the potential for chronic deleterious impact of therapy but not specific to chemotherapy. It was also observed that better scores were associated with improved survival. Similarly in the EORTC study no significant difference in QOL was observed between the two treatment groups outside of the acute treatment interval suggesting no chronic negative impact from the addition of chemotherapy [39].

### Glioblastoma

Previously the survival of patients with newly diagnosed GBM was too short to meaningfully assess the chronic or cognitive impact of relatively ineffective or short-lived therapies. However, increasingly therapies are available which result in meaningful survival as evidenced by the number of long-term survivors.

Assessment of long-term survivors reveals some important observations that may be used to guide future therapeutic strategies [40, 41]. One study of 39 GBM patients with survival of 3y or more following initial diagnosis showed that the majority of patients (85%) had neurologic impairment, including at least 30% with cognitive dysfunction [41]. Nine patients had evidence of a cerebrovascular event, either ischemic or hemorrhagic, and six had radiation-induced necrosis. It is important to consider that most of these patients (72%) had been treated both for their primary diagnosis of GBM as well as for subsequent recurrence with a variety of therapies.

The addition of temozolomide during initial radiotherapy has been the major change in standard of care over the past decade [42]. Patients receiving this treatment have more than double the possibility of surviving at 2 years as compared with patients treated with radiation alone. This treatment approach raises the question of the safety of administration of concomitant chemoradiotherapy. From the long term follow up of the pivotal study of the EORTC there is little evidence to suggest additive or synergistic toxicity resulting from this regimen [43]. Indeed, only three patients out of the original cohort are reported as having late treatment related toxicity at 5 years. Two patients in the concurrent temozolomide and radiotherapy arm had late toxicity—one patient with seizures and another with visual deficit; one patient in the RT alone arm is reported to have fatigue. These results are further supported by a small prospective study from the Netherlands that directly assessed cognitive function in newly diagnosed patients

being treated with this standard therapy [44]. Early assessment during and immediately after the therapy found that most patients were cognitively stable or improved; however, long-term follow up was not available.

This new standard of care is currently under debate for older patients. Patients over the age of 70 were not included in the original EORTC study. This is an important area of consideration because older patients comprise a significant fraction of patients diagnosed with GBM. Furthermore this patient subset typically has a worse prognosis and may be more vulnerable to the negative effects of therapy. Several studies and reports have now demonstrated that concomitant TMZ/RT may be an effective therapy in older patients [45–48]. However a recent prospective study suggests that there may be a significant risk of toxicity among older patients treated with this regimen [46]. Fifty-eight patients over the age of 65 were treated with the standard of care and achieved excellent progression free and overall survival (9.5 and 13.7 months, respectively) as compared with historic controls; however, 25% of patients developed grade 3–4 cognitive dysfunction and 10% developed leukoencephalopathy. The authors concluded that this rate of toxicity may be unacceptably high and merits further study prior to recommending this regimen as standard of care in older patients. Several other reports have raised similar concerns of excess toxicity among older patients treated with concurrent temozolomide and RT [47, 48]; an ongoing intergroup study will provide prospective data with regard to efficacy and toxicity in this population [49]. Of interest, a recent prospective study of temozolomide alone for frail patients over 70 years of age showed improvement of QOL and cognitive function in responding or stable patients [50].

A recent study looked at neurocognitive outcome as an exploratory endpoint for a trial of bevacizumab in recurrent glioblastoma [51]. Using three standardized tests of specific cognitive domains the researchers were able to demonstrate that neurocognitive status (worsened, stable, or improved) correlated with radiographic tumor response and disease control as measured by progression free survival. This data suggests the possibility of incorporating neurocognitive testing as an alternate measure of efficacy to support imaging criteria. Neuro-cognitive function is being used as an endpoint in several ongoing clinical trials of new therapies for brain tumors.

### Conclusions

At the present time there is little evidence to support a serious concern for the risk of “chemo brain” among patients with a primary brain tumor. While the acute impact of chemotherapy may result in fatigue and apparent

cognitive decline during the course of active therapy, available data suggests that most patients with a positive response to chemotherapy will also have cognitive stability or improvement to mirror the anti-tumor effect. Data regarding the long-term cognitive impact of chemotherapy remains sparse. The best data from patients with PCNSL do not support significant delayed or chronic neurotoxicity induced by chemotherapy. Long term follow up of patients with anaplastic oligodendroglioma that fail to suggest any incremental decline in function among patients treated with chemotherapy in addition to RT; but detailed cognitive assessment following chemotherapy is not available for these patients or those with low grade glioma. Emerging data related to elderly patients with glioblastoma merit additional study to exclude significant neurotoxicity as a result of concomitant temozolomide and radiotherapy. Our primary charge continues to be the discovery of more effective therapies to control primary brain tumors as the major risk to cognitive function at present is the presence of active tumor either at diagnosis and recurrence.

**Conflict of interest statement** The author declares that she has no conflict of interest.

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